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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/801,852	03/08/2001	Shu-Jen David Chiang	ON0163NP	6300
23914	7590	03/31/2005	EXAMINER	
STEPHEN B. DAVIS BRISTOL-MYERS SQUIBB COMPANY PATENT DEPARTMENT P O BOX 4000 PRINCETON, NJ 08543-4000			SLOBODYANSKY, ELIZABETH	
			ART UNIT	PAPER NUMBER
			1652	
DATE MAILED: 03/31/2005				

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)
	09/801,852	CHIANG ET AL.
	Examiner	Art Unit
	Elizabeth Slobodyansky, PhD	1652

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) Responsive to communication(s) filed on 27 December 2004.
 2a) This action is **FINAL**. 2b) This action is non-final.
 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4) Claim(s) 1,3-6 and 8-11 is/are pending in the application.
 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
 5) Claim(s) _____ is/are allowed.
 6) Claim(s) 1,3-6 and 8-11 is/are rejected.
 7) Claim(s) _____ is/are objected to.
 8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9) The specification is objected to by the Examiner.
 10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
 a) All b) Some * c) None of:
 1. Certified copies of the priority documents have been received.
 2. Certified copies of the priority documents have been received in Application No. _____.
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) Notice of References Cited (PTO-892)
 2) Notice of Draftsperson's Patent Drawing Review (PTO-948)
 3) Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
 Paper No(s)/Mail Date _____.

4) Interview Summary (PTO-413)
 Paper No(s)/Mail Date. _____.
 5) Notice of Informal Patent Application (PTO-152)
 6) Other: _____.

DETAILED ACTION

Response filed December 27, 2004 containing Remarks has been entered.

Claims 1, 3-6 and 8-11 are pending.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3-6 and 8-10 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1, 3-6 and 8-10 are drawn to a method of use of a strain of *Acremonium chrysogenum* transformed with a nucleic acid encoding a *Rhodosporidium* cephalosporin esterase. Therefore, these claims recite a genus of nucleic acids encoding a *Rhodosporidium* cephalosporin esterase. This genus encompasses nucleic acids encoding any cephalosporin, including cephalosporin C, esterase from any species and strains of *Rhodosporidium*. Furthermore, said genus encompasses nucleic acids encoding esterases that hydrolyze the acetyl bond on the 10-position of a cephalosporin as well as other(s) position(s).

The Court of Appeals for the Federal Circuit has recently held that a "written description of an invention involving a chemical genus, like a description of a chemical

species, "requires a precise definition, such as be structure, formula [or] chemical name," of the claimed subject matter sufficient to distinguish it from other materials." University of California v. Eli Lilly and Co., 1997 U.S. App. LEXIS 18221, at *23, quoting Fiers v. Revel, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) (bracketed material in original). To fully describe a genus of genetic material, which is a chemical compound, applicants must (1) fully describe at least one species of the claimed genus sufficient to represent said genus whereby a skilled artisan, in view of the prior art, could predict the structure of other species encompassed by the claimed genus and (2) identify the common characteristics of the claimed molecules, e.g., structure, physical and/or chemical characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or a combination of these.

In the instant specification, the genus of nucleic acids encoding a *Rhodosporidium* cephalosporin C esterase is represented by a genomic nucleic acid isolated from a single strain of *Rhodosporidium toruloides* (ATCC 10657) having the nucleotide sequence of SEQ ID NO:1 and corresponding cDNA having the sequence of SEQ ID NO:3. SEQ ID NOs: 1 or 3 encode cephalosporin C esterase of SEQ ID NO:2 that hydrolyzes the acetyl bond on the 10-position of cephalosporin C (Official name Cephalosporin-C deacetylase). No other nucleic acid sequences encoding a *Rhodosporidium* cephalosporin esterase are disclosed in the specification. Moreover, the specification fails to describe any other representative species by any identifying characteristics or properties other than the functionality of encoding a *Rhodosporidium* cephalosporin esterase.

Given this lack of description of representative species encompassed by the genus of the claims, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention, the genus of nucleic acids encoding a *Rhodosporidium* cephalosporin C esterase.

Claims 1, 3- 6 and 8-10 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of use of a strain of *Acremonium chrysogenum* transformed with a nucleic acid encoding a *Rhodosporidium* cephalosporin C esterase of SEQ ID NO:2, including SEQ ID NOs:1 and 3, does not reasonably provide enablement for a method of use of a strain of *Acremonium chrysogenum* transformed with a nucleic acid encoding a *Rhodosporidium* cephalosporin C esterase having an unknown homology to SEQ ID NOs: 1 or 3. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, how to make and/or use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in

the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The specification does not support the broad scope of the claims which encompass nucleic acids having an unknown homology to SEQ ID NOs:1 or 3 and encoding any *Rhodosporidium* cephalosporin C esterase having an unknown homology to SEQ ID NO: 2.

The specification does not teach nucleic acids encoding any *Rhodosporidium* cephalosporin C esterase other than the esterase having the amino acid sequence of SEQ ID NO: 2 encoded by SEQ ID NOs:1 or 3. While recombinant hybridization techniques are known, only highly homologous sequences can be identified using a given nucleic acid sequence. The state of the art provides no reasonable expectation of success in obtaining nucleic acid encoding DHAK having an unknown homology to SEQ ID NO: 1 and the result of such screening is unpredictable.

Without sufficient guidance, beyond that provided, determination of nucleic acids encoding a *Rhodosporidium* cephalosporin C esterase having an unknown homology to SEQ ID NO:2, said nucleic acid having an unknown homology to SEQ ID NOs:1 or 3 is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 3-6 and 9-11 are rejected under 35 U.S.C. 102(b) as being anticipated by Politino et al. (A).

Politino et al. (A), (WO 98/12345, form PTO-1449 filed January 14, 2002, reference AM) teach a DNA encoding cephalosporin C esterase from *Rhodosporidium toruloides* that is 100% identical to SEQ ID NO:3 of the instant invention and differs by one nucleotide from SEQ ID NO:1. They teach the method for producing said cephalosporin C esterase by culturing cells of *Cephalosporin acremonium* transformed with a DNA encoding a cephalosporin esterase from *Rhodosporidium toruloides* (page 9, claims 26-28). The cells must be cultured at conditions that are standard for culturing *Cephalosporin acremonium*. These conditions would include temperature between about 22⁰C to about 29⁰C and the pH is about 5.5 to about 7.5. They further teach that *Cephalosporin acremonium* (*Acremonium chrysogenum*) is producing cephalosporin C and contains nucleic acid encoding enzymes for cephalosporin C biosynthesis. They teach that when a cephalosporin C esterase from *Rhodosporidium toruloides* is added, desacetylcephalosporin C is produced (Example 2). They teach that cephalosporin C is completely hydrolyzed by the esterase within 30 min at 30⁰ C, pH 6.5, with no side products observed by HPLC (page 16, lines 14, 25-26). The conditions of "30⁰ C" that is

"about 29° C" and "pH 6.5" that is in the range of "about 5.5 to about 7.5" meet the limitations for the experimental parameters recited in claim 1.

Therefore, they teach a method for producing of desacetylcephalosporin C by culturing cells of *Cephalosporin acremonium* (*Acremonium chrysogenum*) transformed with a DNA encoding a *Rhodosporidium* esterase.

The teachings of Politino et al. further meet the limitations of the chemical breakdown of cephalosporin C of less than 40%, 30%, 20%, 10% or 5% as required by claims 1 and 3-6 because no side products were observed by HPLC (page 16, Example, 2.1).

A person shall be entitled to a patent unless -

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 1, 3-6 and 9-11 are rejected under 35 U.S.C. 102(e) as being anticipated by Politino et al.(B).

The applied reference has a common assignee with the instant application.

Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

Politino et al. (B), (US Patent 5,869,309, form PTO-1449 filed June 14, 2001, reference AG) is US counterpart of WO 98/12345, *supra*.

Politino et al. (B) teach a DNA encoding cephalosporin C esterase from *Rhodosporidium toruloides* that is 100% identical to SEQ ID NOs: 1 or 3 of the instant invention. They teach the method for producing said a cephalosporin C esterase by culturing cells of *Cephalosporin acremonium* transformed with a DNA encoding a cephalosporin esterase from *Rhodosporidium toruloides* (claims 17-24). The cells must be cultured at conditions that are standard for culturing *Cephalosporin acremonium*. These conditions would include temperature between about 22⁰C to about 29⁰C and the pH is about 5.5 to about 7.5. They further teach that *Cephalosporin acremonium* (*Acremonium chrysogenum*) is producing cephalosporin C and contains nucleic acid encoding enzymes for cephalosporin C biosynthesis. They teach that when a cephalosporin C esterase from *Rhodosporidium toruloides* is added, desacetylcephalosporin C is produced (Example 2). They teach that cephalosporin C is completely hydrolyzed by the esterase within 30 min at 30⁰ C, pH 6.5, with no side

products observed by HPLC (column 9, line 60, through column 10, line 14). The conditions of "30° C" that is "about 29° C" and "pH 6.5" that is in the range of "about 5.5 to about 7.5" meet the limitations for the experimental parameters recited in claim 1.

Therefore, they teach a method for producing of desacetylcephalosporin C by culturing cells of *Cephalosporin acremonium* (*Acremonium chrysogenum*) transformed with a DNA encoding a *Rhodosporidium* esterase.

The teachings of Politino et al. further meet the limitations of the chemical breakdown of cephalosporin C of less than 40%, 30%, 20%, 10% or 5% as required by claims 1 and 3-6 because no side products were observed by HPLC (column 9, line 60, through column 10, line 14).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claim 8 is rejected under 35 U.S.C. 103(a) as being unpatentable over Politino et al. (A) or (B) in view of Smith et al.

The teachings of Politino et al. (A) and (B) are outlined above.

Smith et al. (US Patent 4,533,632, form PTO-1449 filed June 14, 2001, reference AC) teach a process for the preparation of desacetylcephalosporin C by fermenting

Acremonium chrysogenum in the presence of esterase from *Rhodosporidium toruloides* (claims 1-7). The process of fermentation is carried out at 15°-45° C and pH 4-9.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use *Acremonium chrysogenum* transformed with a DNA encoding *Rhodosporidium toruloides* esterase in the production of desacetylcephalosporin C. This would allow to increase and standardize the production of the esterase used in the method taught by Smith et al. Such host cells are taught by Politino et al. (A, B). It would have been further obvious to find and use optimal conditions for producing of desacetylcephalosporin C and fermenting *Acremonium chrysogenum* within the range of standard conditions taught by Smith et al.

Response to Arguments

Applicant's arguments filed December 27, 2004 have been fully considered but they are not persuasive.

With regard to the 112, 1st written description rejection, Applicants argue that "the present invention is not claiming *Rhodosporidium cephalosporin* esterase, rather it is directed to a process for the direct production of desacetylcephalosporin C using the stated fungal organism. Accordingly, one of skill in the art would readily be able to determine which *Rhodosporidium cephalosporin* esterases are capable of satisfying the conditions of the claims. Obviously, any such esterase not satisfying the conditions of the present claims would not be within the scope of the present invention" Remarks, page 4). This is not agreed with because the Court reasoned

that the written description requirement of 35 U.S.C. §112 ¶1 cannot be satisfied by merely providing the desired function of the compound without more detail on the compound's structure, chemical formula, chemical name, or physical properties. The court also stresses the applicability of the written description requirements to the compound used, even though the patent consists of method claims rather than compound claims. *University of Rochester v. G.D. Searle & Co. Inc.* Page 427.

In the instant case that the claimed method entails the use of the compound, a nucleic acid encoding *Rhodosporidium* cephalosporin esterase. The genus of said esterases comprises various cephalosporin esterases, including the subgenus *Rhodosporidium* cephalosporin C esterases, of which a cephalosporin C esterase from *Rhodosporidium toruloides* (ATCC 10657) is disclosed. No correlation between structure of this representative species and other members of the genus is disclosed.

With regard to the 112, 1st enablement rejection, "Applicants again respectfully point out that the present invention is not claiming *Rhodosporidium cephalosporin* esterase, rather it is directed to a process for the direct production of desacetylcephalosporin C using the stated fungal organism. Accordingly, one of skill in the art would readily be able to determine which *Rhodosporidium cephalosporin* esterases are capable of satisfying the conditions of the claims. Obviously, any such esterase not satisfying the conditions of the present claims would not be within the scope of the present invention" (page 4, last paragraph). this is not persuasive because the claim is not drawn to the method of use a cephalosporin C esterase

from *Rhodosporidium toruloides*, i.e. to a cephalosporin C esterase of SEQ ID NO:2 or a highly homologous sequence, but to a method of use of any cephalosporin esterase from *Rhodosporidium* that cannot be obtained using a DNA encoding cephalosporin C esterase from *Rhodosporidium toruloides* of SEQ ID NO:2.

With regard to the 102 (b, e) rejections, Applicants argue "The Examiner continues to rely on Politino (A), which describes the cloning and sequencing of *R. toruloides* cephalosporin esterase genomic and cDNA genes. However, it does not disclose *Acremonium chrysogenum* containing both a nucleic acid encoding enzymes for cephalosporin C biosynthesis and a recombinant nucleic acid encoding *Rhodosporidium cephalosporin* esterase which is capable of directly fermenting desacetylcephalosporin C wherein there is less than 40% loss of cephalosporin C due to non-enzymatic breakdown". Applicants continue "The Examiner alleges that Example 2 in Politino (A) states that because no side products were observed with HPLC, this satisfies the requirement that less than 40% of cephalosporin C is lost. However, Applicants respectfully assed that the Examiner's reliance on Example 2 is misplaced and point out that Example 2 does not disclose the claimed process as required for anticipation, namely the use of the claimed recombinant fungal organism for the fermentation of desacetylcephalosporin C in which the chemical breakdown of cephalosporin C to 2-(D-4-amino-4-carboxybutyl)-thiazole-4-carboxylic acid is less than 40%" (page 5). Applicants continue "the Examiner states that *A. chrysogenum* naturally contains nucleic acids encoding enzymes for cephalosporin C biosynthesis and concludes, therefore, that an *A. chrysogenum* transformed with DNA encoding

cephalosporin esterase will directly produce both cephalosporin C esterase and desacetylcephalosporin C. However, there is no actual disclosure of the claimed process and therefore no basis on which the Examiner can make this conclusion. The Examiner further states that the claimed conditions for culturing *A. chrysogenum* are standard and that the chemical breakdown of cephalosporin C to 2-(D-4-amino-4-carboxybutyl)-thiazole-4-carboxylic acid is less than 40% due to the fact that no byproducts were seen in HPLC in Example 2. However, Applicants again point out that Example 2 of Politino (A) does not disclose a process of the claimed invention, so it is not clear how this is relevant" (page 6).

It appears that Applicants agree with the examiner's description of the art but believe that the preamble of the claim, i.e. the way the method is named makes a difference. However, Applicants use the same transformed cell as used in Politino. The difference is that they used it for the production of desacetylcephalosporin C. However, the claimed method comprises a single step that is the same step as in the method of Politino. Therefore, said preamble is not given a patentable weight.

Applicants argue that "Politino (A) merely discloses the cloning of the esterase gene which is required for heterologous expression of an active enzyme, but it does not necessarily follow that the enzyme will be readily expressed in an active form. In fact, efforts to express this enzyme in an *E. coli* host did not result in an active protein, as describe at pages 37-38 of the present specification. The Examiner dismisses this argument, saying that it is not relevant because the claimed process does not use a transformed *E. coli*, but Applicants submit that this point is very relevant as it shows the

problems which were solved in the process of the present invention (namely, expressing the esterase in a host cell which is described, but not taught in Politino (A)), which further evidences the fact that the suppositions made by the Examiner (namely, that a host cell actually transformed such as in the present invention would be useful in the inventive process) are unfounded " (page 6, emphasis added).

This statement is unclear. Applicants do not indicate how the recombinant host cell of the claimed method is different from the recombinant host cell taught by Politino (A). Applicants do not explain what changes compared to Politino were made in the nucleic acid construct to render the expression of the esterase in active form. Absent any changes, the cell taught by Politino produced the same enzyme in an active form.

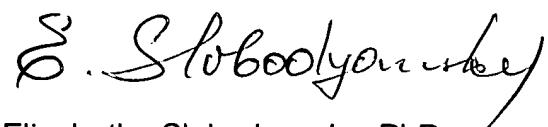
With regard to the 103(a) rejection Applicants argue that " In the outstanding Office Action, the Examiner states that Smith is cited for its disclosure of conditions for culturing of *Acremonium chrysogenum*. However, in the 103 rejection, the Examiner states that it would have been "obvious to use *Acremonium chrysogenum* transformed with a DNA encoding *Rhodosporidium toruloides* esterase in the production of desacetylcephalo4porin C." Therefore, Applicants again submit that the Examiner has not shown why this would be obvious nor provided any motivation to support such an allegation. If Smith is merely being cited for its disclosure of conditions for culturing of *Acremonium chrysogenum*, as stated by the Examiner, it is not understood how this provides the motivation "to use *Acremonium chrysogenum* transformed with a DNA encoding *Rhodosporidium toruloides* esterase in the production of desacetylcephalosporin C" which is the stated rejection under Section 103 " (page 7).

Smith is cited for the entirety of the teachings. It includes the method for the preparation of desacetylcephalosporin C by fermenting *Acremonium chrysogenum* in the presence of esterase from *Rhodosporidium toruloides* (claims 1-7) and the conditions to carry out the process. The claimed method is different from the method taught by Smith in that the esterase is recombinantly produced by the cell whereas in the method of Smith, the esterase is added to the cell. Politino makes the requisite cell producing the esterase available. Both references render the claimed method obvious because it would have been obvious to use *Acremonium chrysogenum* transformed with a DNA encoding *Rhodosporidium toruloides* esterase in the production of desacetylcephalosporin C as opposed to adding the esterase to a non-transformed cell because this would allow to increase and standardize the production of the esterase used in the method taught by Smith et al. in a 103(a) rejection neither reference have to disclose the same invention but only to make it obvious.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Elizabeth Slobodyansky, PhD whose telephone number is 571-272-0941. The examiner can normally be reached on M-F 10:00 - 6:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, PhD can be reached on 571-272-0928. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Elizabeth Slobodyansky, PhD
Primary Examiner
Art Unit 1652

March 25, 2005